Genetic and Environmental Influences on Stuttering and Tics in Japanese Twin Children

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The purpose of this study was to clarify the genetic contribution to stuttering and tics in childhood using the largest databases of Japanese twins. The subjects were 1896 pairs of twin children consisting of 1849 males and 1943 females with a mean age of 11.6 years (3 years to 15 years). All data were gathered by questionnaire. The prevalence of stuttering was 6.7% in males and 3.6% in females ($p < .0001$). The prevalence of tics was 6.8% in males and 4.1% in females ($p = .0021$). Concordance rates and polychoric correlations were all higher in monozygotic pairs than in dizygotic pairs irrespective of sex combination. Structural equation modeling showed that the proportion of total phenotypic variance attributable to genetic influences was 80% in males and 85% in females for stuttering, and 28% in males and 29% in females for tics. Moreover, co-occurrence between stuttering and tics was observed in 0.8% of males (tetrachoric correlation: $r = .18$) and 0.5% of females ($r = .31$), which was attributed partly (nearly 10% of total genetic variance of each trait) to the common genetic factors, with genetic correlation of $r = .32$.

Stuttering and tics are both puzzling and debilitating traits that often occur in childhood. The prevalence rates of stuttering reported in the literature have been widely divergent, ranging from a low of 0.7% to a high of 15.4% (Felsenfeld et al., 2000). The morbid risk of stuttering is usually cited as 5.0%, a figure reflecting the average across studies. The prevalence rates of tics have also been divergent, ranging from 2.9% to more than 20% of school children (Khalifa & von Knorring, 2003; Kurlan et al., 2002; Lanzi et al., 2004; Snider et al., 2002; Wang & Kuo, 2003). The reason for this variation is unknown, but it partly reflects differences in sample characteristics across studies, for example subject age, sampling methods (interview vs. questionnaire, parental report vs. observation, self-reports vs. reports by others), and subject selection (clinic-based vs. population-based), as well as diagnostic criteria. Both stuttering and tic symptoms always emerge in childhood, usually prior to the age of 10 years. Phenotypic severity and symptom expression are variable. As with many complex behavioral disorders, most stuttering and tic cases in the population are probably mild in severity. Among young children, partial or complete recovery from stuttering or tics is common. Both stuttering and tics are more common in males. Among young children, the gender ratio is approximately 2:1 or more for both stuttering (Felsenfeld et al., 2000) and tics (Snider et al., 2002).

Despite nearly a century of research activity, the etiology of stuttering and tics remains uncertain. Within the last few decades, however, promising findings from behavioral genetic studies have provided evidence that genetic factors may be important in the expression of stuttering (Ambrose et al., 1997; Yairi et al., 1996) and tics (Abe & Oda, 1980; Godai et al., 1976; Price et al., 1985; Wang & Kuo, 2003) in childhood. Of these, twin studies using a large number of subjects have been few in number.

These traits are usually, if anything, normal habits in the broad sense, rather than lasting behavioral problems or disorders. The aim of this study was to clarify the prevalence of stuttering and tics in normally developing twin children in Japan, and the role of genetic and environmental factors in the origin of these traits. These traits have never been analyzed from the genetic viewpoint, at least for a large Oriental twin sample.

Materials and Methods

Outline of the Present Samples

The present sample consisted of volunteer-based Japanese twin databases. These databases were constructed for maternal and childcare purposes with multiples and genetic epidemiologic twin family studies. The basic characteristics of the databases are reported in detail elsewhere (Ooki & Yokoyama, 2004). There were 2082 twin pairs in total, consisting of 951 twin-pair children of mothers in several associations for parents of multiples throughout Japan, and 1131 pairs of applicants to a secondary

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school. The twins ranged in age from 0 to 15 years at the time of data collection.

Zygosity Classification

The zygosity of the twins was determined primarily by a questionnaire (Ooki & Asaka, 2004) that has been used widely in Japan and that, in the present study, was completed by the mothers in both groups. Zygosity — monozygotic (MZ), unclassified (UZ), and dizygotic (DZ) — was determined according to similarity scores that were calculated using five questions about physical similarity and the confusion of identity between the twins. The accuracy of classification was nearly 97.5%, although about 10% of the pairs were unclassified. The accuracy was a trade-off according to the percentage of unclassified pairs. For the school applicants group, zygosity was also diagnosed by the use of many genetic markers for those twin pairs who were actually admitted to the school, prior to the administration of the zygosity questionnaire.

As zygosity testing is very rare in Japan, this is the largest twin study sample on behavior genetics in Japan to date that includes specified zygosity.

Data Collection

Mailed or hand-delivered questionnaires were used to collect the data. These included questions about family structure; obstetric findings on the mothers; the twins' physical growth, motor, language, and mental development; the twins' and parents' medical histories; habitual behaviors and any behavioral problems the twins had had.

From these questions, the author analyzed items regarding habitual behavior in childhood, namely stuttering and tics. Mothers identified the frequency of these behaviors from four categories: 'often', 'sometimes', 'never', or 'don't know'. Terms pertaining to stuttering and tics were explained in easily understandable language.

One limitation of the questionnaire survey was that strict medical criteria regarding the definition of these items, such as those found in *Diagnostic and Statistical Manual of Mental Disorders* (APA, 2000) were not used. It would have been difficult to obtain correct answers regarding events and behaviors that had, for some subjects, ceased several years prior to the administration of the questionnaire.

Subjects for Analysis

Not all of the subjects were analyzed, as some twins were too young. The occurrence of behavior traits in the study is generally age-dependent. Only 1896 pairs (1849 males and 1943 females) were analyzed, all of whom were 3 or more years of age. Mean age was 11.6 years and the standard deviation was 1.4 years. Eighty-five pairs (4.48%) were below 10 years of age. The pairs were classified as follows: 1130 MZ, consisting of 537 male–male and 593 female–female pairs; 588 DZ, consisting of 150 male–male, 151 female–female, 146 male–female, and 141 female–male pairs; and 178 UZ, consisting of 94 male–male and 84 female–female pairs.

Statistical Methods

The prevalence of stuttering and tics was calculated according to sex including the subjects of unclassified zygosity. Sex difference was tested by the χ^2 test. Next, genetic analysis was performed using MZ and DZ pairs with both twins' complete frequency data. Twin similarity for ordinary data can be estimated using a concordance rate (McGue, 1992). For the calculation of concordance rates, the answers were summarized in 2×2 contingency tables form ('often' and 'sometimes' were included in one category). The probandwise concordance rate is the proportion of all probands that belong to concordant pairs. Pairwise concordance rates were the proportion of all concordant pairs in all pairs. Probandwise concordance rates were calculated as $2C/(2C + D)$, and pairwise concordance rates were calculated as $C/(C + D)$, where C denotes the numbers of affected concordant pairs and D denotes numbers of discordant pairs.

When the number of unaffected twin pairs is known, a more sophisticated model can be used to estimate the contribution of genetic factors to the susceptibility to the target traits. The polygenic multifactorial model assumes that a latent variable called 'liability to the traits' is normally distributed. When a certain threshold of liability is reached, the traits manifest. Both genes and environmental factors are assumed to contribute to this liability. Namely, the combination of many genes with small effects and a multitude of environmental factors cause the disorder to manifest. The correlation of liability was obtained as polychoric correlation (Neale & Cardon, 1992). This correlation of the latent liability was calculated directly from the 2×2 or 3×3 tables, cross-classifying the affected status of the first and second twin in each twin pair. Basic statistics, concordance rates and polychoric correlations were computed using PC SAS Version 8 (1999).

Structural equation modeling techniques were used to estimate variance components and to compare different genetic models by carrying out standard univariate twin analyses. As the data of opposite-sex DZ twin pairs were obtained, several types of sex-limitation models were analyzed (Neale & Cardon, 1992). These models postulated four sources of variance in liability to the traits: (1) additive genetic effects (A); (2) nonadditive genetic effects (D); (3) common (shared) or family environmental factors (C); (4) individual-specific environmental factors (E). Sex-specific genetic factors A' and D' were also considered. The proportion of the total variance in liability due to additive and nonadditive genetic effects and common and individual-specific environment were termed a^2, d^2, c^2 and e^2 respectively, where a, d, c and e denote each path coefficient from latent variables (A, D, C, E) to observed variables. One can fit models based on the different combinations of these four parameters: ACE, ADE, AE, ACEA', ADEA', ADED', AEA', Scalar ACE, Scalar

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ADE and Scalar AE. The limitation is that the nonadditive genetic effect and the common environmental effect cannot be simultaneously modeled with data from twins reared together (Neale & Cardon, 1992). The best-fitting model was chosen using the information criteria of Akaike (AIC; 1987), the chi-square value minus twice the degree of freedom, which reflects both the goodness-of-fit and the parsimony of the model. The model with the lowest value of AIC reflects the best balance of goodness-of-fit and parsimony. An 'equal environment assumption' for MZ and DZ was adopted according to a previous study by Kendler et al. (1993).

Phenotypic correlations between stuttering and tics were then calculated as polychoric correlations. Finally, bivariate genetic analyses (Neale & Cardon, 1992) were performed. The correlated factors model and the Cholesky decomposition model were utilized for ACE, ADE, AE and CE by taking the results of phenotypic correlations into consideration. Throughout all model-fitting analyses, a goodness-of-fit index (GFI) > .85 was used as the criteria for model adoption. Structural equation modeling was performed by the LISREL8 software package (Jöreskog & Sorbom, 1993).

Ethical Issues

The mothers in the maternal associations group all cooperated voluntarily in this research primarily through the associations. Informed consent regarding the statistical analysis of the school applicant group's data was obtained from each twin and his/her parents in writing as part of the application process.

Results

Prevalence of Stuttering and Tics

The prevalence in each frequency category for the occurrence of stuttering and tics in childhood is given in Table 1. Stuttering and tics were significantly more common in males than in females. Stuttering and tics were not significantly related to zygosity and birth order (i.e., first born, second born etc.; data not shown). Males (compared with females) showed stuttering in childhood 'often' in 0.9% of cases (females in 0.4%) and 'sometimes' in 5.8% (3.2%). Males showed tics in childhood 'often' in 0.8% of cases (females in 0.3% of cases) and 'sometimes' in 6.1% (females 3.8%).

Table 1

Prevalence Rates of Stuttering and Tics According to Sex

		Males	Females	*p*
Stuttering	*N*	1849	1943	
	Often	16 (0.9%)	7 (0.4%)	
	Sometimes	103 (5.8%)	61 (3.2%)	
	Never	1654 (93.3%)	1818 (96.4%)	< .0001
Tics	N	1789	1889	
	Often	12 (0.8%)	5 (0.3%)	
	Sometimes	96 (6.1%)	64 (3.8%)	
	Never	1473 (93.2%)	1607 (95.9%)	.0021
	Missing value	208	213	

Note: Sex difference was tested by χ^2 test.

Concordance in Twin Pairs

Table 2 shows the pairwise and probandwise concordance rates and polychoric correlations (*r*). Pairs in which either twin could not specify the occurrence of stuttering or tic frequency were excluded. All pairwise and probandwise concordance rates of MZ pairs were higher than those observed in DZ pairs. Based on the 2×2 contingency tables, polychoric correlations were computed. The correlations of MZ pairs were higher than those of DZ pairs.

Models of Genetic and Environmental Factors

The results of the univariate genetic analysis are shown in Table 3. An ADE model was selected for stuttering, and an ACE model for tics. The path coefficients and variance components of the best-fitting models are shown in Table 4. In these models, the estimated proportion of total phenotypic variance

Table 2

Concordance Rates and Polychoric Correlations from 3×3 Contingency Table

		MZ			DZ			
		MM	FF	Total	MM	FF	Total (same-sex)	FM
Stuttering	*N*	512	573	1085	141	148	289	278
	Pair-wise	0.34 (16/47)	0.37 (11/30)	0.35 (27/77)	0.05 (1/19)	0.08 (1/12)	0.07 (2/31)	0.05 (1/22)
	Proband-wise	0.51 (32/63)	0.54 (22/41)	0.52 (54/104)	0.10 (2/20)	0.15 (2/13)	0.12 (4/33)	0.09 (2/23)
	Polychoric *r*	.78	.86	.81	.08	.37	.19	.23
Tics	*N*	472	518	990	124	141	265	248
	Pair-wise	0.26 (14/53)	0.18 (7/39)	0.23 (21/92)	0.13 (2/15)	0.08 (1/12)	0.11 (3/27)	0.14 (2/14)
	Proband-wise	0.42 (28/67)	0.30 (14/46)	0.37 (42/113)	0.24 (4/17)	0.15 (2/13)	0.20 (6/30)	0.29 (4/14)
	Polychoric *r*	.64	.57	.62	.43	.30	.37	.53

Note: MZ = monozygotic; DZ = dizygotic; MM = male–male; FF = female–female; FM = female–male

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Table 3

The Results of Sex-Limitation Model

		df	χ^2	*p*	AIC	GFI
Stuttering	ACE	9	24.75	0.00	6.75	0.98
	AE	11	25.70	0.01	3.70	0.97
	ADE	**9**	**2.13**	**0.99**	**–15.87**	**1.00**
Tics	**ACE**	**9**	**15.56**	**0.08**	**–2.44**	**0.95**
	AE	11	36.60	0.00	14.60	0.86
	ADE	9	36.60	0.00	18.60	0.86

Note: A = additive genetic factor; D = dominant genetic factor; C = common environmental factor; E = random environmental factor.
Tetrachoric correlations based on 2 × 2 contingency tables were used for model fitting.

attributed to the genetic component was 80% (A: 9%, D: 71%) in males and 85% (A: 56%, D: 29%) in females for stuttering, and 28% in males and 29% in females for tics. Common environmental factors were observed with tics.

Co-occurrence of Stuttering and Tics in the Same Child

Co-occurrence of stuttering and tics was 0.8% (12/1571) in males and 0.5% (8/1674) in females. Phenotypic correlations (tetrachoric correlation) between stuttering and tics were .18 (n = 1571, p = .0387 for Fisher's exact test) in males and .31 (n = 1674, p = .0043 for Fisher's exact test) in females. Tetrachoric correlations according to zygosity were pooled over sex as only a small sample size had both stuttering and tics. MZ pairs showed higher correlations than DZ pairs with regards to both stuttering (r = .84 vs. r = .20) and tics (r = .66 vs. r = .40). Phenotypic correlations of stuttering and tics in the same individual were relatively high (r = .13 to .46), irrespective of zygosity and birth order. Cross-correlations between stuttering and tics of MZ pairs were slightly higher than those of DZ pairs (r = .26 vs. r = .24; r = .23 vs. r = .21). Bivariate genetic analyses were performed using these correlations. The best-fitting model was the AE model (df = 13, χ^2 = 87.04, GFI = .90). The path coefficients of the best-fitting model are shown in Figure 1. Genetic correlation between stuttering and tics was 0.32. Genetic contribution in common with both traits was around 10% (9% in stuttering and 12% in tics as percentage of total genetic variance in each trait).

Discussion

It is difficult to obtain the accurate prevalence of stuttering and tics in the children population. Habitual traits depend more or less on the age of the subjects. The prevalence of behaviors has varied depending on the report, and it is somewhat difficult to compare the results. The prevalence of traits depends on the sample size, the age of subjects at data collection, methods of measurement, and so on. The prevalence of stuttering and tics found in this study is not so different from previous reports. Moreover, the tendency of higher prevalence in males for both stuttering and tics was also in accordance with that observed in singletons, suggesting the effects of sex difference partly on both traits.

The concordance rates and polychoric correlations were both higher in MZ pairs than in DZ pairs irrespective of sex. The zygosity classification of same-sex twins in childhood has been very rare in Japan. Moreover, zygosity misclassification at birth by means of easy placental findings occurred in 25% to 30% of MZ twin pairs (Ooki et al., 2004). Mothers of same-sex twins, therefore, often did not know the correct zygosity of their children. The zygosity of the present samples, however, was objectively obtained and considerably accurate. Therefore, the higher concordance rates and polychoric correlations in MZ pairs rather than DZ pairs strongly suggest the role of genetic background.

The genetic contributions to stuttering (Ambrose et al., 1997; Yairi et al., 1996) and tics (Abe & Oda, 1978, 1980; Godai et al., 1976) have long been highlighted by classic genetic studies. Of these studies, twin studies have been relatively few in number. Genetic analysis of stuttering was classically performed by Howie (1981) and showed higher concordance rates in MZ pairs. Andrews et al. (1991) and Felsenfeld et al. (2000) recently showed the genetic contribution to stuttering by analyzing a large Australian Twin Cohort. The present study estimated the proportion of total phenotypic variance attributable to the genetic component as 80% (A: 9%, D: 71%) in males and 85% (A: 56%, D: 29%) in females for stuttering; these findings were very similar to those of Andrews et al. (1991) which esti-

Table 4

The Results of Sex-Limitation Model

		Path coefficients								Variance component (%)							
		a_m	c_m	d_m	e_m	a_f	c_f	d_f	e_f	A_m	C_m	D_m	E_m	A_f	C_f	D_f	E_f
Stuttering	ADE	.30		.84	.45	.75		.54	.38	9		71	20	56		29	15
Tics	ACE	.53	.64		.56	.54	.57		.63	28	41		31	29	32		39

Note: m = male; f = female.

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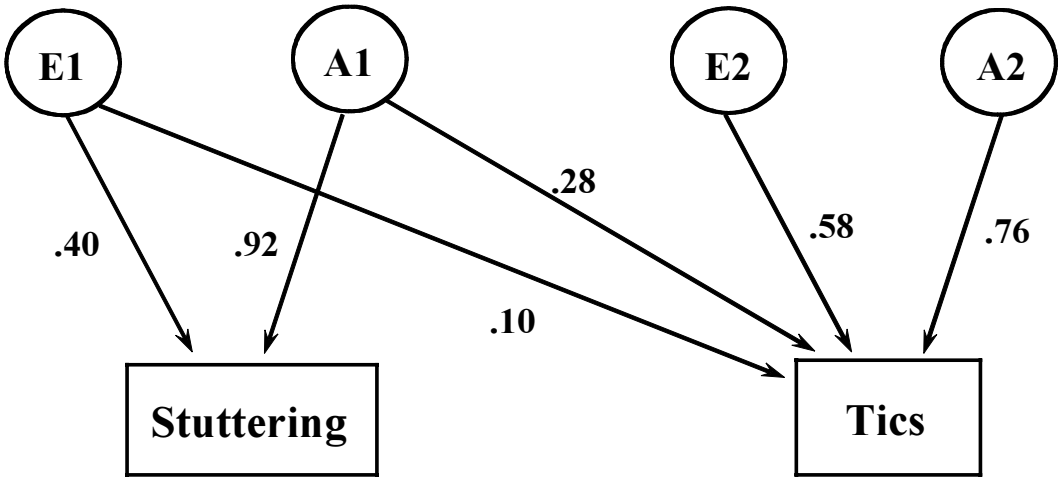

Figure 1

Path coefficient of best-fitting Bivariate Cholesky Decomposition Model.
Variance components are calculated by squaring these path coefficients. In the case of stuttering, for example, genetic contribution to the total variance is estimated to be 84% (= $0.92^2/[0.92^2 + 0.40^2] \times 100$).

mated the genetic contribution to stuttering as 73%, including a large proportion of nonadditive genetic factors (D) in males (A: 13%, D: 60%).

Twin studies of tics have in the most part been performed as part of the genetic analysis for Tourette syndrome, a common disorder in children and adolescents which has tics as one of the main symptoms. Twin studies focusing on tics in the broad sense have been very limited. Both Godai et al. (1976) and Price et al. (1985), for example, showed higher concordance rates in MZ than in DZ pairs, although subject numbers were small. The present study supports these results. Structural equation modeling showed that the proportion of total phenotypic variance attributable to genetic influences is 28% to 29% for tics. The contribution of common environmental factors to tics was observed for both sexes, with a slightly higher proportion in males.

Although classic studies have shown genetic contributions, few have considered gender difference as a result of small sample sizes and as only concordance rates were calculated. As information from opposite-sex DZ pairs was included in this study, direct detection of sex-specific effects by structural equation modeling was permitted.

Stuttering and tics do co-occur in both males and females, although this frequency was lower than 1%. The tetrachoric correlation between stuttering and tics in females (r = .31) was slightly higher than in males (r = .18). To the author's knowledge, a twin study of stuttering and tics with the same subjects has only been previously performed by Godai et al. (1976), with 63 twins pairs with one or both of the pair affected by stuttering and/or tics. A stronger genetic contribution to the occurrence of stuttering (pair-wise concordance in 10:12 MZ and in 2:19 DZ) rather than tics (pair-wise concordance in 6:10 MZ and in 2:22 DZ) was shown. The present study also showed a higher genetic contribution to stuttering rather than tics irrespective of sex. Bivariate genetic analysis estimated the genetic correlation between stuttering and tics at .32. About 10% of the genetic contribution to each trait was estimated by common genetic factors. Stuttering is often studied as part of the behavioral manifestations of Tourette syndrome. Comings and Comings (1987) found that Tourette syndrome patients had a significantly increased stuttering frequency when compared to the random normal control. On the other hand, Pauls et al. (1993) found no evidence that stuttering represents a variant expression of Tourette syndrome. Tourette syndrome is thought to be associated with attention deficit hyperactivity disorder, obsessive–compulsive disorder, and a number of other psychiatric disorders (Pringsheim et al. 2003).

Twin studies will be a powerful tool in analyzing genetic contributions to the phenotypic correlations or comorbidity of many behaviors, including problem behaviors in childhood (Schmitz & Mrazek, 2001). Further systematic twin study should be performed on a wide range of phenotypic correlations, including stuttering and tics.

This study has several limitations. First, the prevalence was calculated by retrospective maternal reports only, not by observation — some unexpected bias may be involved. Second, the age effect was not taken into consideration. Since behavior characteristics in childhood vary greatly with age, it is desirable to increase the accuracy of information about age of occurrence and duration of stuttering and tics. The age of 95.5% of the present sample was 10 years or more; these subjects had, for the most part, already moved beyond the target behaviors. The results should be interpreted as

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the average genetic influence in childhood. Third, the total MZ/DZ ratio of the present sample was 1.92 (1130/588), the upper limit of the recent Japanese MZ/DZ ratio (Imaizumi & Nonaka, 1997), which decreased from 1.90 in 1979 to 1.09 in 1994.

In spite of these limitations, the present study indicated significant genetic effects on the occurrence of stuttering and tics. The genetic effect was higher in stuttering than tics. In addition, it suggests that the etiology of the co-occurrence of both stuttering and tics was, in part, attributable to the common genetic background of the two traits.

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